## Claims

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                     peptide having natriuretic activity of the
     formula:
          R<sup>1</sup>-Cys-Phe-Gly-Arg- Arg/ - Leu/ -Asp-Arg-Ile-
                                Lys
                                       Met
10
                                                                 (1)
             Gly/ -Ser- Deu/ -Ser-Gly-Leu-Gly-Cys-R2
             Ser
    wherein R^1 is selected from the group consisting of:
15
                                                           (H);
                                                          Gly-;
                                                      Ser-Gly-;
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                                               Asp/
                                               Lys/ -Ser-Gly-;
                                               Gly
                                       Arg/
                                               Asp/
                                       His
                                               Lys/ -Ser-Gly-;
                                       Gln
                                               Gly
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                                       Arg/
                                               Asp/
                               Met/ - His/
                                              Lys/ -Ser-Gly-;
                                       Gln
                               Val
                                               Gly
                                               Asp/
                                       Arg/
                        Thr/ - Met/ - His/ - Lys/ -Ser-Gly-;
                                               Gly
                        Met
                               Val
                                       Gln
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                                       Arg/
                                               Asp/
                  Lys- Thr/ - Met/ - His/ - Lys/
                                                     -Ser-Gly-;
                        Met
                               Val
                                       Gln
                                               Gly
                                       Arg/
                                               Asp/
              Pro-Lys- Thr/ - Met/ - His/
                                            - Lys/
                                                    -Ser-Gly-;
                        Met
                               Val
                                       Gln
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                                               Gly
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Ser-Pro-Lys-\Thr/ - Met/ - His/ - Lys/ -Ser-Gly-;
Met Val Gln Gly
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or a 10- to 109-amino acid sequence shown as the native upstream sequence for porcine, canine or human BNP in Figure 8, or a composite thereof;

 $R^2$  is (OH),  $\backslash NH_2$ , or NR'R" wherein R' and R" are independently lower alkyl (1-4C) or is

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Asn/ Lys

Asn/ -Val Lys

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Asn/ -Val-Leu Lys

Asn/ -Val-Leu-Arg Lys

Asn/ -Val-Leu-Arg- Arg

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or the amides (NH, or NR'R") thereof,

with the proviso that if formula (1) is

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R<sup>1</sup>-Cys-Phe-Gly-Arg-Arg-Leu-Asp-Arg-Ile-Gly-Ser-Leu-Ser-Gly-Leu-Gly-Cys-R<sup>2</sup>

and R<sup>1</sup> is Asp-Ser-Gly-, R<sup>2</sup> cannot be Asn-Val-Leu-Arg-Arg-Tyr.

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2. A peptide having natriuretic activity which is a modified form of the peptide of claim 1, having conservative amino acid substitutions in one or two positions.

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The peptide of claim 1 having the formula:
                 R<sup>1</sup>-Cys-Phe-Gly-Arg-Arg-Leu-Asp-Arg-
                     Ile-Gly-Ser-Leu-Ser-Gly-Leu-Gly-Cys-R2
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     wherein R<sup>1</sup> is selected from Thr-Met-Arg-Asp-Ser-Gly; Ser-
     Pro-Lys-Thr-Met-Arg-Asp-Ser-Gly; and Gly-Ile-Arg-Ser-Pro-
     Lys-Thr-Met-Arg-Asp-Ser-Gly; and the 10- to 108-amino acid
     upstream sequence shown for porcine prepro-BNP in Figure
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     8.
                     The peptide of claim 1 having the formula
                 4.
                 R<sup>1</sup>-Cys-Phe-Gly-Arg-Arg-Leu-Asp-Arg-
Ile-Gly-Ser-Leu-Ser-Gly-Leu-Gly-Cys-R<sup>2</sup>
     wherein R<sup>1</sup> is selected from
                                             Lys-Ser-Gly-
                                        His-Lys-Ser-Gly-;
                                   Met-His-Lys-Ser-Gly-;
                               Met-Met-His-Lys-Ser-Gly-;
2.0
                          Lys-Met-Met-His-Lys-Ser-Gly-;
                Pro-Lys-Met-Met-His-Dys-Ser-Gly-;
Ser-Pro-Lys-Met-Met-His-Lys-Ser-Gly-;
     and the 10- to 109-amino acid sequence shown for canine BNP
     in Figure 8.
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                     The peptide of claim 1 having the formula
                R<sup>1</sup>-Cys-Phe-Gly-Arg-Lys-Met-Asp-Arg-
                    Ile-Ser-Ser-Ser-Gly-Lew-Gly-Cys-R2.
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                     The peptide of claim 5 wherein R is selected
                6.
    from
                                                 Ser-Gly
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                                            Gly-Ser-Gl
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Gln-Gly-Ser-Gly-;
Val-Gln-Gly-Ser-Gly-;
Met-Val-Gln-Gly-Ser-Gly-;
Lys-Met-Val-Gln-Gly-Ser-Gly-;
Pro-Lys-Met-Val-Gln-Gly-Ser-Gly-;
Ser-Pro-Lys-Met-Met-His-Lys-Ser-Gly-;
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and the 10- to 109-amino acid sequence shown for human BNP in Figure 8.

- 7. A recombinant DNA in isolated form consisting essentially of a DNA which encodes the peptide of claim 1.
- 8. A recombinant expression system capable, when contained in a recombinant host cell, of expressing the DNA encoding the peptide of claim 1.
  - 9. A recombinant host cell or cell culture which has been manipulated so as to contain the expression system of claim 8.

10. A method to produce a peptide having natriuretic activity, which method comprises:

culturing the cells of claim 9 under conditions which permit the expression of the DNA encoding said 25 peptide; and

recovering the peptide from the culture.

- 11. A pharmaceutical composition useful in treating conditions associated with a high level of extracellular fluid which composition comprises an effective amount of the peptide of claim 1 in admixture with a suitable pharmaceutical excipient.
- 12. A method to treat a condition characterized 35 by a high level of extracellular fluid which comprises administering to a subject in need of treatment an effec-

tive amount of the peptide of claim 1 or a pharmaceutical composition thereof peptide.

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  13. The method of claim 12 wherein the condition is congestive heart failure.
- treating conditions associated with a high level of extracellular fluid which composition comprises an effective amount of the peptide of claim 6 in admixture with a suitable pharmaceutical excipient.
- by a high level of extracellular fluid which comprises administering to a subject in need of treatment an effective amount of the peptide of claim 6 or a pharmaceutical composition thereof.
- 16. The method of claim 15 wherein the condition is congestive heart failure.
- encoding brain natriuretic peptide from a vertebrate DNA
  library, which probe comprises the pBNP-encoding cDNA shown in Figure 1, or an effective portion thereof.
- 18. A DNA sequence encoding a peptide having natriuretic activity, which DNA hybridizes directly or indirectly with the probe of claim 17 at 42°C in buffer containing 20% formamide, 5 x Denhardt's, 6 x SSC, 100 mg/ml RNA, 0.05% Na pyrophosphate, followed by washing at 60°C at 1 x SSC, 0.1% SDS.
- 19. A peptide having natriuretic activity encoded by a DNA, which DNA hybridizes directly or in-

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directly with the probe of claim 17 at  $42^{\circ}$ C in buffer containing 20% formamide, 5 x Denhardt's, 6 x SSC, 100 mg/ml RNA, 0.05% Na pyrophosphate, followed by washing at  $60^{\circ}$ C at 1 x SSC, 0.1% SDS.

with the proviso that said peptide is not pBNP.

- 20. A DNA sequence which comprises a segment of contiguous or non-contiguous portions of the cDNA of Figure 1, which segment encodes a brain natriuretic peptide having natriuretic activity.
  - 21. The DNA of claim 20 wherein the segment encodes pBNP.
  - 22. The DNA of claim 20 wherein the segment encodes the peptide sequence Thr-Met-Arg-pBNP.
- 23. The DNA of claim 20 wherein the segment encodes the peptide sequence Ser-Pro-Lys-Thr-Met-Arg-pBNP.
  - 24. The DNA of claim 20 wherein the segment encodes the peptide sequence Gly-Ile-Arg-Ser-Pro-Lys-Thr-Met-Arg-pBNP.
- 25. A DNA sequence which comprises a modified segment of contiguous or non-contiguous portions of the cDNA of Figure 1 wherein said modified segment encodes a BNP having one or two conservative amino acid substitutions.
  - 26. A recombinant expression system which comprises the segment of claim 20 operably linked to control sequences functional in a recombinant host.

- 27. A recombinant host transformed with the expression system of claim 26.
- 28. A method to produce a recombinant brain natriuretic peptide which comprises culturing the transformed host of claim 27 under conditions suitable for the expression of the BNP and,

recovering BNP from the culture.

29. Recombinant BNP produced by the method of claim 28, with the proviso that said BNP is not pBNP.

modification of a BNP encoded by a segment of contiguous or non-contiguous portions of the CDNA of Figure 1 wherein one or two positions contain conservative amino acid substitutions.

31. The BNP of claim 30 wherein one of said substitutions is substitution of the D- for the L-form.

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add A3)

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